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REMARKS

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Status Summary

Claims 1-50 are pending. Claims 2, 6, and 8-50 are withdrawn as being directed to non-elected inventions. Claims 1, 3-5, and 7 are under examination. Claims 1, 3-5, and 7 remain rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to teach methods that enable one skilled in the art to practice the invention commensurate in scope with the claims. Claims 1 and 7 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Maloney et al. (1997) *Blood* 90:2188-2195 (Maloney). Claims 1, 5, and 7 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Maloney in view of U.S. Patent No. 5,626,845 to Yoneda et al. (Yoneda). Claims 1, 3-5, and 7 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. in view of Murphy et al., eds. (1995) Clinical Oncology, 2nd edition, American Cancer Society, Atlanta, Georgia, in view of Kuppers et al. (1998) *Ann Oncol* 9 (Suppl 5):S17-20, and further in view of Yoneda. Claims 1, 3, 5, and 7 are also rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al.

Claims 2, 6, and 8-50 are canceled. Claim 1 is amended and new claims 51-60 are added. Reconsideration in view of the claim amendments and following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 1, 3-5, and 7 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable one skilled in the art to practice the invention commensurate in scope with the claims. Specifically, it is the examiner's opinion that the claims enable a method of treating an established CNS lymphoma, but do not support prophylaxis of CNS lymphoma. Official action, at pages 2-3. This rejection is respectfully traversed.

Claim 1 is amended to affirmatively state that the anti-CD20 antibodies are administered to a subject diagnosed with a CNS lymphoma. This amendment is made to facilitate prosecution and is not a concession that the prophylactic methods of applicant's invention are not enabled by the instant disclosure. Applicant believes that claim 1 is fully enabled by the specification in accordance with the requirements of 35 U.S.C. § 112, first paragraph. Claims 3-5 and 7 ultimately depend from claim 1 and are therefore also believed

to fully comply with 35 U.S.C. § 112, first paragraph. Thus, applicant respectfully requests that the rejection of claims 1, 3-5, and 7 under § 112, first paragraph, be withdrawn.

Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 1 and 7 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Maloney et al. (1997) *Blood* 90:2188-2195 (Maloney). The examiner has rejected applicant's arguments that CNS lymphomas are pathologically distinct from systemic lymphomas and require distinct therapeutic approaches as unpersuasive. In the view of the examiner, the applicant has not provided evidence to conclude that the treated non-Hodgkin's lymphoma as described by Maloney is not inclusive of a CNS lymphoma. Official action, pages 3-4. This rejection is respectfully traversed.

Maloney describes anti-CD20 therapy in patients with relapsed low-grade non lymphoma (*see* title and abstract). Maloney does not describe administration of anti-CD20 antibodies to a patient with CNS lymphoma.

Applicant responds that a *prima facie* case of anticipation has not been made because Maloney fails to describe every element of the subject claims. As noted herein above, claim 1 is amended to clarify that the anti-CD20 antibodies are administered to a subject diagnosed with a CNS lymphoma. The methods of Maloney, which are directed to treatment of low-grade non-Hodgkin's lymphoma are not inclusive of methods for treatment of CNS lymphoma as suggested by the examiner. Specifically, low-grade lymphomas are histologically and pathologically distinct from aggressive lymphomas, such as CNS lymphoma. *See e.g.*, Hoppe (1987) *Curr Probl Cancer* 11:363-447 (abstract, submitted previously). The U.S. National Cancer Institute (NCI) classifies low grade or follicular B cell lymphomas as "indolent," and the majority of aggressive lymphomas are classified as diffuse large cell lymphoma. *See* ---- (1982) The non-Hodgkin's lymphoma pathologic classification project: National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage, *Cancer* 49:2112-2135 (submitted herewith) and Harris et al. (1994) A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group, *Blood* 84:1361-1392 (submitted herewith). These classifications are significant, given that methods for treating low grade or indolent lymphomas, as in Maloney, are often ineffective for the treatment of aggressive lymphomas, such as CNS lymphomas. *See e.g.*, Plotkin & Batchelor (2000) *Clin Lymphoma* 1(4):263-275. In addition, treatment of CNS

lymphomas may require administration (*e.g.*, intrathecal administration) and dosing techniques suitable for delivery of therapeutics across the blood-barrier. These considerations are absent from Maloney. Thus, the presently claimed methods for treatment of a CNS lymphoma, an aggressive lymphoma, is not anticipated by Maloney, which only describes administration of anti-CD20 antibodies to subjects having low-grade lymphoma.

Based on the foregoing arguments, applicant believes that claims 1 and 7 are patentably distinguished over Maloney. Applicant thus requests that the rejection of claims under 35 U.S.C. § 102(b) be withdrawn.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1, 5, and 7 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Maloney et al. (1997) *Blood* 90:2188-2195 (Maloney) in view of U.S. Patent No. 5,626,845 to Yoneda et al. (Yoneda). This rejection is respectfully traversed. Claims 1, 3-5, and 7 are further rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of Murphy et al., eds. (1995) Clinical Oncology, 2nd edition, American Cancer Society, Atlanta, Georgia (Murphy), further in view of Kuppers et al. (1998) *Ann Oncol* 9 (Suppl 5):S17-20 (Kuppers), and still further in view of Yoneda. This rejection is also respectfully traversed.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. Applicant responds that the examiner has failed to meet this burden. Applicant further responds that the presently claimed methods are unexpected and thereby non-obvious over the cited references.

With regard to the rejection of claims based on Maloney, applicant reiterates that the present invention is patentably distinguishable over Maloney, as set forth above. In particular, Maloney fails to teach or suggest anti-CD20 therapy of a subject having aggressive lymphoma, and more particularly, a CNS lymphoma. The examiner relies on Yoneda for the teaching that antibody fragments such as Fab, Fab', and F(ab')2 are art-known substitutes for antibodies. First official action (paper no. 7), page 7. Thus, Yoneda does not cure the deficiency of Maloney, *i.e.*, by describing or suggesting anti-CD20 therapy of a subject

having aggressive lymphoma such as CNS lymphoma, to thereby render obvious the methods of the present invention. Based thereon, applicant respectfully requests that the rejection of claims under 35 U.S.C. § 103(a) based on Maloney and Yoneda be withdrawn.

With regard to the rejection of claims based on Anderson, as allegedly evidenced by Murphy, Kupper, and Yoneda, applicant responds that the unexpected results of the present invention support the non-obviousness of the methods now claimed. The Court of Appeals for the Federal Circuit has repeatedly held that secondary considerations such as unexpected results can effectively rebut a finding of *prima facie* obviousness. *See e.g.*, *In re Geisler*, 116 F.3d 1465, 1469, 43 U.S.P.Q.2d 1362 (Fed. Cir. 1997) (quoting *In re Soni*, 54 F.3d 746, 750, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995). Thus, even assuming *arguendo* that a *prima facie* case of obviousness has been established, the unexpected qualities of the presently claimed combination are sufficient to overcome the examiner's finding.

Anderson describes methods for treatment of B cell lymphoma via administration of anti-CD20 antibodies. The examiner notes that Anderson does not teach treatment of CNS lymphomas, as now claimed. The examiner relies on Murphy as teaching that most primary CNS lymphomas are B-cell lymphomas, on Kuppers as teaching that Hodgkin's disease typically involves B cells, and on Yoneda as teaching that antibody fragments such as Fab, Fab', and F(ab')2 are art-known substitutes for antibodies. The examiner concludes that it would have been *prima facie* obvious to modify the methods of Anderson to "include B-cell lymphomas of the central nervous system because such lymphomas merely represent species of the broadly claimed genus of B-cell lymphomas." First official action (paper no. 7), pages 10-12.

Applicant responds that the examiner has ignored known clinically relevant differences among lymphomas, including non-Hodgkin's lymphomas. *See e.g.*, ---- (1982) *Cancer* 49:2112-2135 (submitted herewith), Harris et al. (1994) *Blood* 84:1361-1392 (submitted herewith), and Hoppe (1987) *Curr Probl Cancer* 11:363-447 (submitted previously). Also as noted herein above, existing methods for treatment of lymphoma are often ineffective in the case of aggressive lymphoma, such as CNS lymphoma. In particular, Plotkin states that "[t]he management of [primary central nervous system lymphoma] is quite different from the usual treatment of either primary brain tumors or systemic [non-Hodgkin's lymphoma]." *See* Plotkin & Batchelor (2000) *Clin Lymphoma* 1(4):263-275 (submitted previously). This difference is based in part on different administration and dosing

approaches for delivery of therapeutics across the blood-brain barrier. Thus, treatment of a CNS lymphoma, as now claimed, is unexpected despite successful treatment of non-CNS lymphomas via anti-CD20 therapy.

Based on the foregoing arguments, applicant believes that claims 1, 3-5, and 7 fully comply with the requirements of 35 U.S.C. § 103(a) and request that the rejection of claims 1, 3-5, and 7 based on Anderson and evidenced by Murphy, Kuppers, and Yoneda be withdrawn.

Rejection of Claims Based on Non-Statutory Obviousness-Type Double Patenting

Claims 1, 3-5, and 7 are also rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson). This rejection is respectfully traversed. Based on the arguments set forth above in response to the rejection of claims under 35 U.S.C. § 103(a), which are incorporated herein, applicant believes that the methods of the present disclosure are non-obvious in view of Anderson. As such, applicant also requests that the obviousness-type double patenting rejection be withdrawn.

Discussion of New Claims

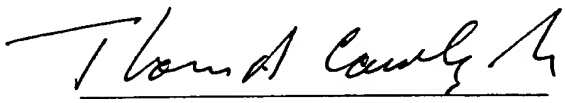
New claims 51-60 are added to describe additional aspects of the invention. Specifically, new claims 51-55 are directed to methods for treating CNS lymphoma whereby growth of a CNS lymphoma is reduced. New claims 56-60 are directed to methods for treating CNS lymphoma whereby the cerebrospinal fluid (CSF) levels of the anti-CD20 antibody or fragment thereof are greater than the serum levels of the anti-CD20 antibody or fragment thereof. Support for the claims can be found in the specification as originally filed, for example at page 65, lines 29-30, wherein it is described that therapeutic end points include morphometric and histologic correlates of anti-lymphoma activity, and at page 66, lines 25-27, wherein it is described that therapeutic end points includes levels of anti-CD20 antibody are greater in CSF than in serum.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP



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